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**Quality of life measurement in hidradenitis suppurativa. Literature review and position statement of the European Academy of Dermatology and Venereology Task Forces on Quality of Life and Patient Oriented Outcomes and Acne, Rosacea and Hidradenitis Suppurativa**

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***Conflict of interest***

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**Abstract**

This paper is organized jointly by the European Academy of Dermatology and Venereology (EADV) Task Force (TF) on Quality of Life (QoL) and Patient Oriented Outcomes and the EADV TF on acne, rosacea and hidradenitis suppurativa (ARHS). The purpose of this paper is to present current knowledge about QoL assessment in HS, including data on HS-specific health-related (HR) QoL instruments and HRQoL changes in clinical trials, and to make practical recommendations concerning the assessment of QoL in people with HS.

HS results in significant impact that is higher than in most other chronic skin diseases. HS impact in published studies was assessed predominantly (84% of studies) by the Dermatology Life Quality Index (DLQI). There is a lack of high quality clinical trials in HS patients where HRQoL instruments have been used as outcome measures. One double-blind randomized placebo-controlled trial on infliximab with low number of participants reported significantly better HRQoL improvement in the treatment group than in the placebo group. Well-designed clinical studies in HS patients to compare different treatment methods, including surgical methods and assessing long-term effects are needed. Because of lack of sufficient validation, the Task Forces are not at present able to recommend existing HS-specific HRQoL instruments for use in clinical studies. The EADV TFs recommend the dermatology-specific DLQI questionnaire for use in HS patients. The EADV TFs encourage the further development, validation and use of other HS-specific, dermatology-specific and generic instruments but such use should be based on the principles presented in the previous publications of the EADV TF on QoL and Patient Oriented Outcomes.

## **Introduction**

Hidradenitis suppurativa/acne inversa (HS) has been, since its first description in 1839 by Velpeau,<sup>1</sup> a medical stepchild due to late diagnosis, lack of effective therapeutic regimens and no clear attachment to a specific medical specialty. Until recently there has been very little scientific interest in the disease. However the establishment by dermatologists and patients of the Hidradenitis Suppurativa Foundation, Inc. in 2005 and of the European Hidradenitis Suppurativa Foundation e.V. in 2012, the first widely accepted definition of the disease being agreed at the 1<sup>st</sup> International Conference on HS Research on 2006 in Dessau, Germany<sup>2</sup>, the establishment of simple diagnostic criteria<sup>3</sup>, guidelines for treatment<sup>4</sup>, classification and follow-up criteria<sup>5-7</sup> and the resulting interest of the pharmaceutical industry<sup>8</sup> has catapulted HS among the diseases with the most growing scientific interest. From 1981 to 2005 there were about 15 publications on HS

identified on PubMed per year. In contrast from January 2017 to June 2018 there were 453 publications (302 per year).

Despite the recent focus on HS education and research, there is still a delay of seven years on average before the diagnosis is correctly made<sup>9</sup>, increasing the likelihood of widespread scarring. The long term aims of understanding HS pathogenesis and the stratification of patients according to their probable response to treatment, as well as the identification of biomarkers as predictive factors for individual treatment, requires robust relevant molecular studies. There has recently been the prospect of more effective treatment with the emergence of various biologics. Currently a core domain outcome set has been described by the Hidradenitis Suppurativa Core Outcomes Set International Collaboration (HISTORIC).<sup>10</sup>

Clinical signs and the secondary effects on daily and social life of HS patients often cause significant impairment of health-related quality of life (HRQoL). Previous reviews on HS underlined the high impact of disease on patients' lives and the absence of HS-specific HRQoL instruments.<sup>11-16</sup> This present paper is organized jointly by the European Academy of Dermatology and Venereology (EADV) Task Force (TF) on QoL and Patient Oriented Outcomes and the EADV TF on acne, rosacea and HS (ARHS). The purpose of this paper is to present current knowledge about QoL assessment in HS, including data on HS-specific HRQoL instruments and HRQoL changes in clinical trials, and to make practical recommendations concerning the assessment of QoL in people with HS.

## **Methods**

Members of the EADV TFs on QoL/PO and ARHS were invited to participate. A literature search was performed using the PubMed database, which was searched from 1980 to September 2018 using the key word combinations: "hidradenitis suppurativa, quality of life" and "acne inversa, quality of life". All publications written in English or those having English abstracts

were considered. All those who volunteered were allocated a section of the identified articles to review.

Exclusion criteria:

- Review articles, guidelines, protocols
- Studies without HRQoL assessment
- Measurement of HRQoL in conditions other than HS
- Studies where HRQoL was measured in patients with conditions other than HS but some of whom may also have acne
- Studies where HRQoL was studied in HS and other diseases but results on HS were not presented and/or discussed separately

All publications were independently assessed by two co-authors. The assessments were compared and discrepancies discussed and resolved. The remaining publications were analyzed in detail and the QoL instruments used in HS were listed. For publications on HS treatment with no data on mean HRQoL scores, where possible the mean scores of the instruments used were calculated using the data of individual patients. The percentage mean change of HRQoL scores from baseline was calculated for each HS treatment method from data given in the included articles, as in a previous EADV Task Force study.<sup>17</sup> The two-tailed paired t-test was used to compare mean scores before and after treatment, with results considered significant if  $p < 0.05$ . The EADV Task Force on QoL and Patient Oriented Outcomes recommends using the word “quimp”<sup>18</sup> (quality of life impairment) in routine clinical work and research<sup>19</sup> and the word has been used in this article.

## Results

From the 212 articles identified in the literature search, 142 were excluded based on the exclusion criteria, leaving 70 publications for the final analysis. Of these 70, the number published each year is presented in Figure 1. In the first, published in 2001,<sup>20</sup> the HRQoL of 160 HS patients was studied using the Dermatology Life Quality Index (DLQI). The highest scoring

DLQI item (question 1) asked about pain, soreness, stinging or itching of the skin. The mean total DLQI score was 8.9, meaning a moderate effect on the patient's life, according to the DLQI score band descriptors.<sup>21</sup> Mean DLQI scores in subsequent HS studies from different countries also reflected a moderate or very large effect on patients' lives (Figure 2). The first study<sup>20</sup> made the prescience suggestion that the DLQI may be a relevant outcome measure in future therapeutic trials in HS. The first such trial, published in 2006, described the efficacy of etanercept in symptom control in six patients with HS.<sup>22</sup> Numerous studies on HS treatment have been published since.

### ***Clinical trials in HS***

We identified seven clinical trials of infliximab,<sup>23-29</sup> six of adalimumab,<sup>30-35</sup> three of etanercept<sup>22,36,37</sup> and two of ustekinumab.<sup>38,39</sup> There were five publications on surgical treatment,<sup>40-44</sup> one study on combination of surgical treatment with photodynamic therapy<sup>45</sup> and two other studies on photodynamic therapy.<sup>46,47</sup> There were three studies on antibiotics,<sup>48-50</sup> single studies on metformin,<sup>51</sup> PUVA,<sup>52</sup> hyperbaric oxygen therapy,<sup>53</sup> alitretinoin,<sup>54</sup> acitretin,<sup>55</sup> ankinra,<sup>56</sup> apremilast,<sup>57</sup> oral zinc gluconate combined with topical triclosan<sup>58</sup> and verapamil.<sup>59</sup> Detailed information on clinical trials that included ten or more HS patients are presented in Table 1. The percentage mean change of HRQoL scores following treatment are given in Figure 3.

There were four double-blind randomized placebo-controlled trials reported in HS with HRQoL assessment as an outcome measure. In a study of infliximab the mean DLQI improvement was significantly better in the treatment group than in the placebo group. The mean DLQI score changes were higher than the minimal clinically important difference (MCID)<sup>60</sup> in the treatment group and lower than the MCID in the placebo group.<sup>23</sup> In a study of etanercept there was no significant difference between the mean DLQI score of the treatment group (10 patients) compared to the placebo group.<sup>37</sup> In the first study on adalimumab (15 patients) mean DLQI was



not significantly worse than at the baseline.<sup>32</sup> The second publication was a post hoc analysis of the 2 phase 3 studies, pioneer I and II on adalimumab.<sup>34</sup> HS patients with good clinical results had lower (better) DLQI scores and more of them had a DLQI score change that was greater than the MCID. One open-label, randomized controlled study on HS treatment with antibiotics and hyperbaric oxygen therapy (22 patients) or antibiotics alone (21 patients) showed significant improvement in DLQI scores that was greater than the DLQI MCID in both groups. However, the difference in QoL changes between the two groups was probably not significant. Other studies had an open-label design. In consequence, only one double-blind randomized placebo-controlled study<sup>23</sup> has shown significantly better improvement of HRQoL scores in the treatment group than in the placebo group. However, a limitation of that study was the low number of patients.

### ***Comparison of QoL in HS, other diseases and controls***

People with self-reported HS and other skin diseases had more impaired HRQoL than the general population.<sup>61</sup> The QoL impact of HS was much greater than the impact of several other dermatologic conditions.<sup>62</sup> Patients with HS have a higher HRQoL burden than patients with psoriasis.<sup>63</sup> Compared with an age-standardized general population, HS patients scored significantly worse on several dimensions of the generic 15D questionnaire. A significant difference compared to psoriasis patients was detected on the sexual activity dimension.<sup>64</sup> Patients with HS had significantly decreased EQ-5D scores in all age groups except for 65-74 year olds.<sup>65</sup> The DLQI was used in parallel with the Major Depression Inventory questionnaire:<sup>66</sup> HRQoL was significantly more impaired in HS patients than in controls but the rate of depression was not significantly higher in HS patients compared to controls. Patients with HS presented significantly higher anxiety, depression, loneliness and social isolation scores and lower self-esteem scores than healthy controls.<sup>67</sup>

### ***Correlation of QoL and disease severity in HS patients***

There was strong positive correlation between DLQI scores and HS clinical severity.<sup>68</sup> Further analysis revealed a slight but statistically significant positive correlation between DLQI scores and the number of skin areas involved with HS lesions. The mean DLQI score for patients with anogenital involvement was  $14.7 \pm 7.2$ , whereas the mean score for other locations was  $9.5 \pm 7.6$ . HS was estimated as having a large or extremely large effect on the patient's life in nearly 60% of patients examined.<sup>68</sup> The severity of disease, as measured by Hurley staging and the number of lesions, significantly correlated with the DLQI scores.<sup>69</sup> QoL, as assessed with the DLQI, was also significantly different among patients in different Hurley stage groups.<sup>70</sup> Pruritus and pain intensity significantly correlated with DLQI scores.<sup>71</sup>

### ***Studies on QoL and sexual problems in HS patients***

The DLQI was used in studies on sexual health of HS patients.<sup>72,73</sup> HS patients had more sexual dysfunction and sexual distress compared to matched controls. Sexual distress was higher in female than in male HS patients.<sup>72</sup> Female sex and late onset of HS were associated with poor sexual function. Impairment of HRQoL was associated with anogenital involvement.<sup>73</sup> In contrast, in another study there was no difference in DLQI scores between men and women. Male patients had higher sexual dysfunction and reduced QoL when compared to a control group. There was no significant difference between female patients with HS and controls regarding sexual functioning. The presence or absence of genital lesions in both male and female HS patients did not correlate with changes in DLQI scores or any sexual function measures.<sup>74</sup>

### ***Validation of HS clinical severity and response instruments***

QoL instruments were used in several studies in the cross-validation of several novel HS clinical severity and response instruments: Hidradenitis Suppurativa Score (HSS),<sup>75</sup> Hidradenitis Suppurativa Clinical Response (HiSCR),<sup>76</sup> Acne Inversa Severity Index (AISI)<sup>77</sup> and International Hidradenitis Suppurativa Severity Score System (IHS4).<sup>7</sup>

### ***Validation of HS-specific QoL instruments***

The initial validation of two HS-specific HRQoL instruments was reported.<sup>78,79</sup> These HS-specific instruments are described in detail below.

### ***Other findings related to QoL assessment in HS patients***

There was no differences in quimp between HS patients with different body mass index and between smokers and non-smokers with HS.<sup>5</sup> HS patients had low physical and social functioning scores when assessed with the generic SF-36 HRQoL questionnaire.<sup>80</sup> A high Hurley stage and female gender were variables that significantly correlated with the total DLQI score in a Finnish study of HS patients.<sup>81</sup> Women in that study had consistently higher scores than men for every item of the DLQI. There was no significant correlation between resilience and HRQoL in HS patients from US and Denmark.<sup>82</sup> Profound impact on the HRQoL of Irish HS patients was reported, including diminished work productivity and various psychological comorbidities.<sup>83</sup> The severity of odour in HS patients was associated with total Skindex-29 scores but not with DLQI scores.<sup>84</sup> In an international study of the QoL impact of treatment (the last DLQI item), over half of HS patients reported problems.<sup>85</sup> The relationship of serum zinc levels with QoL and disease severity in HS was studied: low zinc levels were associated with  $DLQI \geq 9$ .<sup>86</sup> Self-reported depression, anxiety and impaired QoL were strongly associated in HS with illness perceptions.<sup>87</sup> QoL impairment was considered to be a predictor of the self-evaluated health status of HS patients.<sup>88</sup>

### ***HRQoL instruments***

Generic, dermatology-specific and HS-specific HRQoL instruments have all been used in HS (Figure 4). The DLQI was the most frequently used, in 84% of included studies. The second most frequently used instrument was another dermatology-specific questionnaire, Skindex-29 (9% of studies). The DLQI is the most widely used HRQoL instrument in dermatology. It is a

simple 10-question questionnaire covering six domains: Symptoms and feelings, Daily activities, Leisure, Work and School, Personal relationships and Treatment. Responses are on a 4-point Likert scale: the higher the score, the more QoL is impaired. Test-retest reliability, internal consistency, construct validity, responsiveness, score band descriptors and MCID have been described for the DLQI. For general inflammatory skin conditions a change in DLQI score of at least 4 points is considered clinically important.<sup>89,90</sup>

Three HS-specific HRQoL instruments were identified. One was used in the assessment of efficacy of infliximab treatment in two Danish patients with severe fistulizing HS.<sup>24</sup> This unnamed measure was a non-validated 10-item questionnaire focused on perianal problems (6 of 10 items) that was adopted from an instrument used for Crohn's disease.

Another HS-specific questionnaire was developed based on interviews with 21 patients and the opinions of three experts: it was modified after pilot testing in nine patients. Responses are on a 5-point Likert scale and higher scores indicate a worse QoL.<sup>91</sup> Based on results of preliminary validation in 55 HS patients the number of items of the HS-QoL was reduced from 53 to 44, resulting in a seven subscales: Physical consequences, HS symptoms, Sexual activity consequences, Emotional consequences, Social consequences, Work consequences and Social support. The HS-QoL has a 6-months recall period. Internal consistency and convergent validity of the HS-QoL questionnaire were checked.<sup>78</sup>

The third HS-specific HRQoL instrument, the Hidradenitis Suppurativa Burden of Disease (HSBOD), was developed based on interviews with patients (number of patients not presented) and eight dermatologists.<sup>79</sup> The HSBOD is a 19-item questionnaire with 5 domains: Symptoms and feelings, Daily activities, Leisure, Work/school and Personal relationships. Responses are on a 10-cm visual analog scale (VAS). It is divided into two parts with different recall periods: the last 4 weeks (14 items) and the entire time of having HS (5 items). The internal consistency and

convergent validity of the HSBOD questionnaire were checked in studies that included 29 HS patients.

## **Discussion**

HS results in significant quimp that is higher than in most other chronic skin diseases. Pain and HS symptoms have the highest influence on HRQoL. The social and sexual life of patients may be severely affected. In some studies female HS patients and those with genital involvement experienced higher quimp.

Several studies showed that, after initial improvement, the HRQoL of HS patients may worsen again.<sup>31,33</sup> It seems that surgical treatment has the best effect on the HRQoL of HS patients over a long-term perspective. There is a lack of well-organized placebo controlled clinical trials with sufficient participant numbers that assess different treatment methods.

Several reports have advocated the importance of HS-specific HRQoL instruments.<sup>11,15</sup> Some HRQoL measures used in HS have been based on a mixture of clinician opinion, literature review and patient input. However, the question content of HRQoL measures should ideally be based solely on the actual experiences of patients, as is the case for the most widely used instruments in dermatology. This is perhaps why those instruments have been so widely accepted worldwide.<sup>92</sup> In order for QoL measurement to be carried out routinely in a busy clinic, it is essential that the measure used be short, easy to understand, able to be completed unaided and have a simple method of scoring.<sup>92</sup> In this context the HSBOD with 19 items could be potentially more practical than the HS-QoL with 44 items. However, the combination of two different recall periods in a single instrument, as in the case of the HSBOD, may complicate interpretation and especially responsiveness of the instrument's scores. Only the first 14 items of the HSBOD may be used as an outcome measure to assess response to intervention, as the other five items record lifetime experience. The length of the six months recall period of the HS-QoL questionnaire, while gathering more information, may introduce response bias and precludes frequent use.<sup>93</sup>

Two of the HS-specific instruments use different scoring systems, the Likert scale and the visual analogue scale (VAS). Single VAS questions can, in some questionnaires of uniform construct, replace a single Likert item and also be comparable, but not interchangeable, with multi-item Likert indices.<sup>94</sup> Children prefer the Likert scale over the VAS and find it easier to complete.<sup>95</sup> An acknowledged limitation of the HSBOD is that it requires abstract thinking, which may be difficult for some patients.<sup>79</sup>

Recommendations for treatment strategy based on HS severity and HRQoL changes, as is now standard in psoriasis, may be beneficial. This approach was already taken concerning long-term adalimumab efficacy in HS patients.<sup>35</sup>

The position statement of the EADV TFs is that “HRQoL assessment should be widely used in the management of HS patients.” However there is a lack of high quality clinical trials in HS patients where HRQoL instruments have been used as outcome measures. Well-designed clinical studies in HS patients to compare different treatment methods, including surgical methods and assessing long-term effects are needed. Because of lack of sufficient validation, the Task Forces are not at present able to recommend existing HS-specific HRQoL instruments for use in clinical studies. The EADV TFs recommend the dermatology-specific DLQI questionnaire for use in HS patients. The DLQI’s MCID may be used as a marker of minimal treatment efficacy and the DLQI of 0-1, corresponding to “no effect on patient’s life” according to the DLQI banding descriptions, may be considered as a difficult to reach but important treatment goal. The EADV TFs encourage the further development, validation and use of other HS-specific, dermatology-specific and generic instruments but such use should be based on the principles presented in the previous publications of the EADV TF on QoL and Patient Oriented Outcomes.<sup>96-100</sup>

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Figure 1. Number of included publications on QoL in HS per year

Figure 2. Mean DLQI scores in studies on HS from different countries

Figure 3. The percentage mean change of DLQI scores following treatment

Figure 4. How many times each HRQoL instrument was used in HS

Table 1. Information on clinical trials with HRQoL assessment that included ten or more HS patients